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(54) **Pharmaceutical compositions containing peptides of the cholecystokinin-cerulein group for the therapy of shock conditions and of respiratory and cardiocirculatory insufficiencies.**

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Description

The present invention refers to pharmaceutical compositions for the treatment of shock conditions and of respiratory and cardiocirculatory insufficiencies, comprising, as the active principle, a therapeutically effective amount of a polypeptide of the group cholecystokinin-cerulein, selected from cholecystokinin and the fragments thereof comprising the sequence 26-33 (CCK-8), gastrin and all the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and cerulein. Cerulein and cholecystokinin are mostly used during the performance of cholecystographies and cholangiographies and (usually in combination with secretin) in order to assay the pancreatic function. Gastrin is used to assay the stomach secretive capacity. J. Pharm. Exp. Ther. 224, 408, 1983 discloses the effects of the intracerebral administration of cholecystokinin in the normal cat. From Naunyn-Schmiedberg's Arch. Pharmacol. 319, 161, 1982, it is known that caerulein, as well as morphine, is able to counteract the hypotension induced by the pressure increase on the renal pelvis.

As it is well-known, the shock is a clinical condition essentially characterized by an insufficient tissue perfusion, with usually serious hypotension which, if not treated, is generally fatal. Shock may be caused by different causes, such as serious hemorrhages, cranial trauma, dangerous cardiac insufficiency as in certain myocardial infarcts, anaphylactic reactions, etc.

The therapy used at the present time, which is not suited for all kinds of shock, turns out to be unsatisfactory.

Generally, in all shock conditions, there is a tendency to restore the blood volume by means of blood, plasma, saline or glucose solutions or plasma substituents infusion; or to administer oxygen.

However, in serious shock conditions, said treatment is usually insufficient if not even counteracting. In fact, in the cardiogenic shock, infusion of liquids will overload the heart, whose function is already seriously impaired because of the insufficient myocardial contractility.

Administration of vasoconstrictor drugs, such as noradrenaline, adrenaline, metaraminol, mephentermine, in order to increase pressure, often causes the opposite effect, since, under shock conditions (with the exclusion of the neurogenic shock) a severe sympathetic reflex vasoconstriction is already present, whereby tissular perfusion would be further impaired.

On the contrary, administration of drugs such as dopamine, dobutamine, isoproterenol, glucagon, etc. which improve cardiac inotropism without substantially increasing the peripheral resistances, is preferred, particularly in case of cardiogenic shock.

On the other hand, in some instances, administration of vasodilating drugs such as nitroprussiate and α-blockers may be convenient, in order to improve tissue perfusion.

Notwithstanding corticosteroids are widely used in the treatment of shock, no convincing proofs are available supporting the effectiveness of said drugs.

Recently, the efficacy of naloxone in different models of shock has been also studied. Although naloxone turned out to be effective in restoring normal blood pressure values, it is absolutely contraindicated in the shock due to overdose. It is in fact known that naloxone administration to narcotic addicted subjects is followed by a typical abstinence syndrome.

Now it has been surprisingly found that the use of the polypeptides of the group cholecystokinin-cerulein is dramatically effective in the therapeutic treatment of shock (hypovolemic, cardiogenic, traumatic, toxic and anaphylactic shocks), cardiovascular collapse, acute hypotension and respiratory insufficiency, independently from the traumatic, psychogenic, toxic and drug overdose causes.

For instance, in the hypovolemic shock, which is always fatal when the blood loss exceeds 50% of the total blood volume, said polypeptides of the cholecystokinin-cerulein are able to restore to the normal values cardiac output, arterial pressure and breath frequency and amplitude. This effect starts to appear already a few minutes after intravenous injection, it reaches the maximum within 15-20 minutes, it is dose-dependent and require no simultaneous infusion of blood or plasma substitutes.

Even when used as analeptic, said polypeptides show, remarkable advantages in comparison with known analeptics. In fact, all the up to now available analeptics are convulsivant agents used at sub-convulsive dosages, and therefore with a very low therapeutic index and poor handling characteristics; moreover, said polypeptides normalize the circulatory and respiratory functions if they are depressed, without changing them when they are normal.

Said polypeptides are substantially non-toxic and devoid of remarkable side effects.

An object of the present invention is therefore provided by a pharmaceutical composition for the therapeutic treatment of shock conditions and of respiratory and circulatory insufficiencies comprising:

(1) as the active principle, a therapeutically effective amount of a peptide selected from

(a) gastrin

(b) the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and

(c) the oligopeptide consisting exclusively of the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide.

(2) a pharmaceutically acceptable excipient.

Another object of the invention is provided by the use of caerulein or of cholecystokinin or fragments thereof comprising the sequence 26-33 (CCK-8) for the preparation of a medicament for the treatment of shock conditions and of respiratory and cardiocirculatory insufficiency conditions.

Administration of said polypeptides will be preferably carried out by the intravenous route in the shock conditions and by nasal inhalation when the polypeptides are used as analeptics.

In any case, it has been found that the therapeutically effective dose is comprised from about 5 to about 20 μg of said polypeptides per kg body weight.

A suitable pharmaceutical composition to be administered parenterally, in form of a unit dosage, will comprise from 0,5 to 2 mg of said polypeptides and a pharmacologically acceptable excipient.

The above mentioned composition will be generally extemporaneously prepared by the physician or by the patient. The commercially available pharmaceutical form will be therefore a preparation in unit dosage form comprising a vial containing from 0,5 to 2 mg of polypeptide and a vial containing a pharmaceutically acceptable solvent for said polypeptide.

When used as an analeptic for the treatment of respiratory and cardiocirculatory insufficiencies the pharmaceutical composition according to the invention will be in an appropriate form for administration by the inhalatory route, for example as a nasal spray, and it will therefore comprise a therapeutically effective amount of a polypeptide and a gaseous or vaporizable pharmaceutically acceptable excipient. The choice of the most suitable excipients is within the skilled in the art's reach.

The effectiveness of said polypeptides in the treatment of shock has been confirmed by several tests on animals and by clinical studies. Some of said tests and the obtained results are reported hereinafter.

TESTS ON EXPERIMENTAL ANIMALS

Intact and adrenalectomized female Wistar rats (Nossan, Correzzano, Milano, Italy) weighing 250 to 300 g were used. Following anesthetization and heparinization a common carotid artery and an iliac vein were cannulated in rats. Arterial blood pressure was recorded by means of a pressure transducer (Statham P23 Db) connected to a polygraph (Battaglia-Rangoni, Bologna, Italy). In some rats, trachea was cannulated and respiration was recorded by means of a transducer (Statham 10272) connected to the same polygraph. Hypovolemic shock was produced by intermittently withdrawing blood from the venous catheter until mean arterial pressure fell to 10-25 mm Hg. The volume of blood removed was 2-2.5 ml per 100 g of body weight and approximated to, or even exceeded, 50% of the estimated total blood volume. Following bleeding and mean blood pressure stabilization in the range of 10-25 mm Hg, animals were given intravenous bolus of the polypeptides. Control animals were intravenously injected with the same volume of saline (0.1 ml/100 g).

In Figures 1-3 some representative recordings are reported, while the Table shows the data from some tests.

From the examination of the recordings and data it is evident that the intravenous injection of polypeptides dose-dependently restores blood pressure and pulse amplitude, the effect starting within a few minutes, gradually increasing, and reaching a maximum in 15-20 minutes. All rats intravenously injected with the same volume of saline died after about 8-22 minutes.

The results from this study demonstrate that the polypeptides according to the invention increase blood pressure and reverse otherwise fatal hypovolemic shock resulting from massive bleeding.

Although it is not intended neither necessary to rely on any theoretical interpretation to explain the therapeutic effectiveness of the polypeptides in the applications of the present invention, the obtained results, showing that said polypeptides are even more active than naloxone in reversing shock, and that their action is very probably at the CNS level, are consistent with the hypothesis that melanocortins are endogenous antagonists of opioids, and give further experimental support to the suggested existence of a melanocortin-opioid peptidergic system, with a wide functional meaning and with homeostatic, regulatory roles in many, important functions of the body.

In the light of the present results, the hypothesis that shock, rather than the consequence of a massive activation of endogenous opioid system, is the final effect of the melanocortin-opioid homeostasis with prevalence of the opioid component, should be formulated.

With reference to the diagrams illustrates in the drawings:

Fig. 1 shows the effect of a saline solution (s), 0.1 ml/100 g body weight, on the blood pressure after serious hypotension induced by bleeding in the intact rat;

Fig. 2 shows the effect of fragment (CCK-8) of cholecystokinin, 20 µg/kg i.v. on the blood pressure after serious hypotension induced by bleeding in the adrenalectomized rat;

Fig. 3 shows the effect of cerulein (Ce), 20 µg/rat i.v. on the blood pressure after serious hypotension induced by bleeding in the intact rat.

TABLE 1 - Effect of saline, cholecystokinin (CCK-8) and cerulein, treatment on mean arterial pressure, respiratory rate and survival, following severe hypotension induced by bleeding

ANIMALS*	TREATMENT AFTER BLEEDING (µg/kg i.v.)	MEAN ARTERIAL PRESSURE (mm Hg; $\bar{m} \pm$ S.E.)		No. of deaths 120 min. after treatment
		Before bleeding	After bleeding	15-30 min. after bleeding	
Rats (12)	Physiol.sol. i.v.	72.43±8.60	17.50±4.36**	18.25±3.91	12
Rats (6)	CCK8, 5	71.17±6.07	11.83±0.79**	26.33±7.05°	2
Rats (5)	CCK8, 10	68.40±4.98	14.00±1.82**	41.80±3.79***	0
Rats (5)	CCK8, 20	72.00±4.67	14.40±0.87**	52.40±2.73***	0
Rats (6)	Cerulein, 20	75.17±6.62	12.17±1.11**	54.67±4.29***	0

* In parentheses the number of animals used;
** P <0.02, at least, versus value before bleeding;
*** P <0.01, at least, versus value after bleeding;
° P <0.05, at least, versus value after bleeding (Student's t-test for paired data).

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A pharmaceutical composition for the therapeutic treatment of shock conditions and of respiratory and cardiocirculatory insufficiencies, characterized by comprising:
   (1) as the active principle, a therapeutically effective amount of a peptide selected from
   (a) gastrin,
   (b) the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and
   (c) the oligopeptide consisting exclusively of the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide.
   (2) a pharmaceutically acceptable excipient.

2. A pharmaceutical composition for parenteral administration in unit dosage form containing from 0.5 to 2 mg of a polypeptide according to claim 1 and a pharmacologically acceptable excipient.

3. A pharmaceutical composition for inhalatory administration, for the treatment of cardiocirculatory and respiratory insufficiencies, comprising a therapeutically effective amount of a polypeptide selected from cholecystokinin and the fragments thereof comprising the sequence 26-33 (CCK-8), gastrin and all the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and cerulein and a gaseous or vaporizable pharmacologically acceptable excipient.

4. A pharmaceutical composition for parenteral administration in unit dosage form for the therapeutic treatment of shock conditions and respiratory and cardiocirculatory insufficiencies comprising a vial containing from 0.5 to 2 mg of a polypeptide of claim 1 and a vial of a pharmaceutically acceptable solvent for said polypeptide as a combined preparation for simultaneous use in therapy.

5. The use of a polypeptide of the cholecystokinincerulein group selected from cholecystokinin and the fragments thereof comprising the sequence 26-33 (CCK-8), gastrin and all the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and cerulein, in the preparation of a medicament for the therapeutic treatment of shock conditions and of respiratory and cardiocirculatory insufficiencies.

6. The use of a polypeptide according to claim 5, in the preparation of a medicament as claimed in claim 3.

7. The use of a polypeptide according to claim 5, in the preparation of a medicament as claimed in claim 4.

Claims for the following Contracting States : AT, GR, ES

1. Process for the preparation of pharmaceutical compositions for the therapeutic treatment of shock conditions and of respiratory and cardiocirculatory insufficiencies, characterized by comprising the step of admixing
   (1) as the active principle, a therapeutically effective amount of a peptide selected from
   (a) gastrin,
   (b) the gastrin fragments comprising the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide and
   (c) the oligopeptide consisting exclusively of the tetrapeptide sequence L-tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamide, with
   (2) a pharmaceutically acceptable excipient.

2. Process according to claim 1, wherein the excipient is a gaseous or vaporizable pharmacologically acceptable excipient.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische Zusammensetzung zur therapeutischen Behandlung von Schockzuständen und respiratorischen und kardiozirkulären Insuffizienzen, dadurch gekennzeichnet, daß diese
   (1) als Wirkstoff eine therapeutisch wirksame Menge eines Peptids, ausgewählt aus
      (a) Gastrin,
      (b) den Gastrinfragmenten, welche die Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid umfassen, und
      (c) dem Oligopeptid, das ausschließlich aus der Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid besteht, und
   (2) einen pharmazeutisch annehmbaren Hilfsstoff umfaßt.

2. Pharmazeutische Zusammensetzung zur parenteralen Verabreichung in Form von Einheitsdosen, dadurch gekennzeichnet, daß sie zwischen 0,5 und 2 mg eines Polypeptids gemäß Anspruch 1 und einen pharmakologisch annehmbaren Hilfsstoff enthält.

3. Pharmazeutische Zusammensetzung zur Verabreichung mittels Inhalation zur Behandlung von kardiozirkulären und respiratorischen Insuffizienzen, dadurch gekennzeichnet, daß sie eine therapeutisch wirksame Menge eines Polypeptids, ausgewählt aus Cholecystokinin und dessen Fragmenten, welche die Sequenz 26-33 (CCK-8) enthalten, Gastrin und allen Gastrin-Fragmenten, welche die Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid enthalten, und Cerulein, und einen gasförmigen oder verdampfbaren, pharmakologisch annehmbaren Hilfsstoff umfaßt.

4. Pharmazeutische Zusammensetzung zur parenteralen Verabreichung in Form von Einheitsdosen zur therapeutischen Behandlung von Schockzuständen und respiratorischen und kardiozirkulären Insuffizienzen, dadurch gekennzeichnet, daß sie eine Ampulle mit 0,5 und 2 mg eines Polypeptids gemäß Anspruch 1 und eine Ampulle mit einem pharmazeutisch annehmbaren Lösungsmittel für oben genanntes Polypeptid als eine kombinierte Zubereitung zur gleichzeitigen Verwendung in der Therapie umfaßt.

5. Verwendung eines Polypeptids aus der Cholecystokinin-Cerulein-Gruppe, ausgewählt aus Cholecystokinin und dessen Fragmenten, welche die Sequenz 26-33 (CCK-8) enthalten, Gastrin und allen Gastrin-Fragmenten, welche die Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid enthalten, und Cerulein, für die Herstellung eines Arzneimittels zur therapeutischen Behandlung von Schockzuständen und respiratorischen und kardiozirkulären Insuffizienzen

6. Verwendung eines Polypeptids gemäß Anspruch 5 zur Herstellung eines Arzneimittels nach Anspruch 3.

7. Verwendung eines Polypeptids gemäß Anspruch 5 zur Herstellung eines Arzneimittels nach Anspruch 4.

Patentansprüche für folgende Vertragsstaaten : AT, GR, ES

1. Verfahren zur Herstellung pharmazeutischer Zusammensetzungen zur therapeutischen Behandlung von Schockzuständen und von respiratorischen und kardiozirkulären Insuffizienzen, dadurch gekennzeichnet, daß dieses die Stufe des Vermischens
   (1) eines Wirkstoffes, nämlich einer therapeutisch wirksamen Menge eines Peptids, ausgewählt aus
      (a) Gastrin,
      (b) den Gastrinfragmenten, welche die Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid enthalten, und
      (c) dem Oligopeptid, das ausschließlich aus der Tetrapeptidsequenz L-Tryptofyl-L-methionyl-L-aspartyl-L-phenylalanylamid besteht, mit
   (2) einem pharmazeutisch annehmbaren Hilfstoff umfaßt.

2. Verfahren gemäß Anspruch 1, dadurch gekennzeichnet, daß der Hilfsstoff ein gasförmiger oder verdampfbarer, pharmakologisch annehmbarer Hilfsstoff ist.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composition pharmaceutique pour le traitement thérapeutique des états de choc et des insuffisances respiratoires et cardiocirculatoires, caractérisée par le fait qu'elle comprend :
   (1) en tant que principe actif, une quantité thérapeutiquement efficace d'un peptide choisi parmi :
   (a) la gastrine,
   (b) les fragments de gastrine comprenant la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide ; et
   (c) l'oligopeptide consistant exclusivement en la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide ;
   (2) un excipient pharmaceutiquement acceptable.

2. Composition pharmaceutique pour l'administration parentérale sous la forme de dose unitaire, contenant de 0,5 à 2 mg d'un polypeptide tel que défini à la revendication 1, et un excipient pharmacologiquement acceptable.

3. Composition pharmaceutique pour une administration par inhalation, pour le traitement des insuffisances cardiocirculatoires et respiratoires, comprenant une quantité thérapeutiquement efficace d'un polypeptide choisi parmi la cholécystokinine et les fragments de celle-ci comprenant la séquence 26-33 (CCK-8), la gastrine et tous les fragments de la gastrine comprenant la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide, et la céruléine, et un excipient gazeux ou vaporisable, pharmacologiquement acceptable.

4. Composition pharmaceutique pour l'administration parentérale sous la forme de dose unitaire pour le traitement thérapeutique des états de choc et des insuffisances respiratoires et cardiocirculatoires, comprenant une ampoule contenant de 0,5 à 2 mg d'un polypeptide tel que défini à la revendication 1, et une ampoule d'un solvant pharmaceutiquement acceptable pour ledit polypeptide en tant que préparation combinée pour une utilisation simultanée en thérapie.

5. Utilisation d'un polypeptide du groupe de la cholécystokinine-céruléine, choisi parmi la cholécystokinine et les fragments de celle-ci comprenant la séquence 26-33 (CCK-8), la gastrine et tous les fragments de la gastrine comprenant la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide, et la céruléine, dans la préparation d'un médicament pour le traitement thérapeutique des états de choc et des insuffisances respiratoires et cardiocirculatoires.

6. Utilisation d'un polypeptide selon la revendication 5, dans la préparation d'un médicament tel que défini à la revendication 3.

7. Utilisation d'un polypeptide selon la revendication 5, dans la préparation d'un médicament tel que défini à la revendication 4.

Revendications pour les Etats contractants suivants : AT, GR, ES

1. Procédé pour la' préparation de compositions pharmaceutiques pour le traitement thérapeutique des états de choc et des insuffisances respiratoires et cardiocirculatoires, caractérisé par le fait qu'il comprend l'étape consistant à mélanger :
   (1) en tant que principe actif, une quantité thérapeutiquement efficace d'un peptide choisi parmi :
   (a) la gastrine,
   (b) les fragments de gastrine comprenant la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide ; et
   (c) l'oligopeptide consistant exclusivement en la séquence tétrapeptidique L-tryptofyl-L-méthionyl-L-aspartyl-L-phénylalanylamide, avec
   (2) un excipient pharmaceutiquement acceptable.

2. Procédé selon la revendication 1, dans lequel l'excipient est un excipient gazeux ou vaporisable, pharmacologiquement acceptable.

Fig. 1

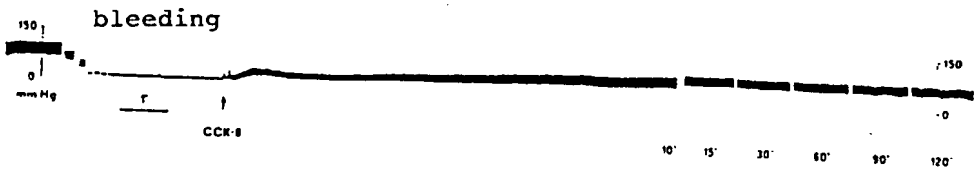

Fig. 2

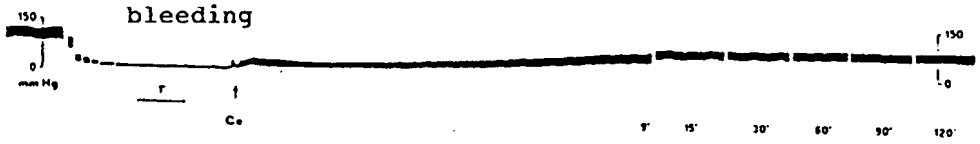

Fig. 3